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## **Risk of Acute Kidney Injury with gentamicin as surgical prophylaxis**

Samira Bell<sup>1,2</sup>

Peter Davey<sup>2</sup>

Dilip Nathwani<sup>3</sup>

Charis Marwick<sup>2</sup>

Thenmalar Vadiveloo<sup>2</sup>

Jacqueline Sneddon<sup>3</sup>

Andrea Patton<sup>3</sup>

Marion Bennie<sup>4</sup>

Stewart Fleming<sup>5</sup>

Peter T. Donnan<sup>2</sup>

<sup>1</sup>Renal Unit, Ninewells Hospital, NHS Tayside, Dundee, UK.

<sup>2</sup>Population Health Sciences Division, Medical Research Institute, University of Dundee, Dundee, UK.

<sup>3</sup>Scottish Antimicrobial Prescribing Group, Scottish Medicines Consortium, Glasgow, UK.

<sup>4</sup>Public Health and Intelligence, National Services Scotland/Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, UK.

<sup>5</sup>Department of Pathology, Division of Cancer Research, University of Dundee, Dundee, UK.

### **Corresponding Author:**

**Samira Bell  
Renal Unit  
Ninewells Hospital  
Dundee  
DD1 9SY**

**Tel: 00 44 1382 633913**

**Fax: 00 44 1382 632327**

**E-mail: [samira.bell@nhs.net](mailto:samira.bell@nhs.net)**

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## Abstract

In 2008 Scottish Government issued a new target to reduce *Clostridium difficile* infection by 30% in three years. Consequently Scottish hospitals restricted antibiotics with high risk for *Clostridium difficile* and changed from cephalosporins to gentamicin for surgical antibiotic prophylaxis. In response to physicians' concerns regarding increasing rates of postoperative acute kidney injury (AKI), this study aimed to examine postoperative AKI before and after the use of gentamicin in surgical prophylaxis.

The study population was all adults undergoing surgery with antibiotic prophylaxis (orthopaedics, urology, vascular, gastrointestinal and gynaecology) between the 1st October 2006 and 30th September 2010. Post-operative AKI was defined by the Kidney Disease Improving Global Outcomes criteria. Study design was an interrupted time series with segmented regression analysis.

12,482 patients were included in the study. In orthopaedic patients, change in policy was associated with a 94% increase in AKI ( $p=0.04$ , 95% CI 93.8- 94.3%). The antibiotic policy change was not associated with significant increase in AKI in any of the other groups. Rates of postoperative AKI in vascular surgery were high at 24%, increased in gastrointestinal surgery steadily throughout the study period and could only be ascertained in 52% urology and 47% gynaecology patients due to lack of creatinine testing.

The change in antibiotic policy from cefuroxime to flucloxacillin (2 doses of 1g) and single dose gentamicin (4mg/kg) was associated with increased rates of AKI in patients undergoing orthopaedic surgery within the Tayside region of Scotland and so should be avoided in orthopaedic patients in the peri-operative period. Our findings also raise concerns about the increasing prevalence of postoperative AKI and of failures to consistently measure postoperative renal function.

## Introduction

Reported rates of post-operative acute kidney injury (AKI) vary due to the heterogeneity of populations studied. Uncomplicated AKI is associated with a mortality of 10% rising to 50% in the context of multi-organ failure and up to 80% if renal replacement therapy (RRT) is required<sup>1, 2</sup>. It was thought that the presence of AKI was a marker of co-existing pathology that increased mortality risk but recent reports demonstrate AKI as an independent risk factor for mortality<sup>3, 4</sup>. The increasing incidence of AKI and its long term consequences has significant socioeconomic and public health impacts globally<sup>5</sup>.

*Clostridium difficile* infection (CDI) is an important healthcare associated infection. Antibiotic use increases the risk of CDI for at least three months<sup>6</sup> and short courses of peri-operative antibiotic prophylaxis have also been associated with increased risk of CDI particularly in the context of an established outbreak<sup>7</sup>.

In 2009 Scottish Government issued a new target for all Health Boards to reduce CDI by at least 50% over two years<sup>8</sup>. The Scottish Antimicrobial Prescribing Group also produced recommendations for all National Health Service (NHS) boards to restrict the use of antibiotics associated with a high risk of CDI<sup>9</sup>. As part of a widespread antibiotic policy change in NHS Tayside; orthopaedic antibiotic prophylaxis was changed from cefuroxime to gentamicin and flucloxacillin. Following concerns raised by nephrologists and a small uncontrolled study in the Dumfries and Galloway region of Scotland which described an increased rate of AKI in patients post orthopaedic surgery following this policy change<sup>10</sup>, it was felt that further investigation of this was required.

The aim of this study was to use robust methodology, in a larger, population-based study of adult patients undergoing orthopaedic implant surgery, to evaluate the effect of the policy change on post-operative AKI. It is noteworthy that patients who underwent repair of fracture neck of femur (NOF) received co-amoxiclav as antibiotic prophylaxis following the policy change due to concerns raised by orthopaedic surgeons with regards to administering gentamicin in this particular patient group. This analysis was then extended to evaluate

postoperative AKI in other surgical specialities (urology, vascular, gastrointestinal and gynaecology) that had changed to a gentamicin based regimen.

## **Results**

### **Descriptive Data**

In total, 12,482 patients were included in the analysis from 1st October 2006 to 30th September 2010. The baseline characteristics of the population are described in Table 1. Of note, within the orthopaedic patient group, 36% of the population were prescribed a NSAID in the year prior to their operation and 38.5% was prescribed a diuretic. When comparing the patients with and without AKI in the orthopaedic group, only increasing Charlson Comorbidity index was associated with increased risk of AKI on multivariate analysis,  $p=0.007$  (95% CI 1.03 to 1.22). There was no difference in the urology patients between patients with or without AKI. In the vascular patients, increasing Charlson Comorbidity index was associated with increased risk of AKI on multivariate analysis,  $p=0.03$  (95% CI 1.08 to 1.42). In the gastrointestinal patients, increasing age and male gender was associated with increased risk of AKI,  $p<0.001$  (95% CI 1.03 to 1.07) and  $p=0.02$  (95% CI 0.39 to 0.91). Increasing age was associated with increased risk of AKI in the gynaecology patients,  $p=0.02$  (95% CI 1.02-1.15).

### **Characteristics of Patients with Missing Data**

Table 2 shows the percentage of available data for each speciality. There were only available biochemistry data pre intervention in 35% of the gynaecology and 58% of urology patients and post intervention in 47% of gynaecology patients and 52% of urology patients. The majority of missing data were missing post-operative serum creatinines rather than pre-operatively. Multivariate analysis of characteristics of included patients versus patients who were excluded due to missing data is shown in Appendix table III. When examining the characteristics of the patients included with the patients who were excluded due to missing data, the orthopaedic patients who were included in the study were older, male gender with

higher comorbidity scores using the Charlson Comorbidity Index as were the gastrointestinal patients.

## **Results of Interrupted Time Series Analysis**

### **Orthopaedic Patients**

Figure 1a shows the percentage of AKI Stages 1, 2 and 3 for each study month. Analyses using ITS showed that there was a significant increase in AKI after the change in prophylactic regimen. After adjustment for use of other nephrotoxic drugs, gender and age, only change in policy was significantly associated with increase in AKI with a significant change in all levels of severity of AKI after the policy change, ( $\beta=0.30$  (95% CI 0.01 to 0.59),  $p = 0.04$ ) for highest serum creatinine post-operatively). This is shown in Table 4.

Patients who underwent repair of fractured neck of femur (NOF) received co-amoxiclav throughout the study period. On analysis of these patients alone, the changes in slope for before and after policy change were virtually zero  $\beta=-0.106$  (95% CI -0.69 to 0.48),  $p = 0.77$  (Figure 1b).

### **Other Surgical Specialities**

Results of ITS analysis are shown in Table 3 for urology, vascular, gastrointestinal surgery and gynaecological surgery. There is no significant increase in the rates of AKI in these surgical specialities related to the policy change. However the baseline rates of AKI in vascular surgery are high at 23.2% but do not increase significantly following the policy change. In gastrointestinal surgery there was a 1.2% monthly increase in AKI ( $p=0.29$ ) before the policy change, with a 0.6% monthly increase after the change in policy, indicating rates that were already rising and slowing after the policy changed.

### **Orthopaedic Outcome data**

A higher proportion of orthopaedic patients with AKI died within one year of surgery compared to those without AKI (20.8% vs 8.2%). Median length of hospital stay was 8 days

(IQR 5-13) in the patients with AKI compared to 7 days (IQR 5- 13) in those without AKI. There were 25 patients with persistent Stage 2 or Stage 3 AKI at seven days post-operatively. None of these patients underwent renal biopsy. Five died during the admission without receiving RRT and 6 received RRT. All surviving patients recovered their renal function to baseline.

## **Discussion**

In this large population based study of over 12,000 patients, we found that increased rates of AKI were associated with change in prophylactic antibiotic policy from cefuroxime to flucloxacillin and gentamicin in patients undergoing orthopaedic surgery (excluding fracture NOF) in the Tayside region of Scotland, UK. The majority of cases had transient Stage 1 AKI but there were persisting cases of Stage 2 and 3. This association with the antibiotic policy change is strengthened as there was no increase in AKI rates in the fracture neck of femur group who received co-amoxiclav as prophylaxis following the policy change. CDI rates fell in both of these groups suggesting that the orthopaedic antibiotic prophylaxis policy change was not responsible for this reduction. We did not find any association between the change in prophylactic antibiotic policy to include gentamicin with AKI in urology, vascular, gastrointestinal and gynaecology surgical patients.

In addition, we identified three areas of concern. Firstly, rates of postoperative AKI in vascular surgery were especially high at 23% pre-intervention and 25% in the post intervention period; secondly rates of postoperative AKI increased in gastrointestinal surgery steadily throughout the study period and thirdly rates of postoperative AKI data could only be ascertained in 52% urology and 47% gynaecology patients because of missing postoperative serum creatinine data.

The strengths of our study are that we addressed risks of bias for ITS studies in our analysis plan (Appendix table 2), defined the operations using OPCS operation codes (Appendix table 1) and used the KDIGO definition of AKI. The limitations of our study are common to all

non-randomised studies, including potential ascertainment and selection biases. Randomised controlled trials are often not appropriate and/or are too expensive to assess the effects of global policy change. ITS is the strongest quasi-experimental design to assess intervention effects in non-randomized settings. It controls for trends existing before the intervention by using multiple points before and after the intervention<sup>11, 12</sup>. A specific limitation of this study was missing pre or post-operative serum creatinines in a large proportion of urology and gynaecology patients. The patients who were included were older and with greater co-morbidity compared to those who were excluded due to missing creatinine data. This could bias the results in these groups in either direction in estimating the rates of AKI. In addition, we were unable to adjust for potential effects of medication and intra-operative events on AKI rates as this data are not collected electronically.

AKI occurs in 5 to 7.5% of acute care hospital in-patients. Of these cases, 30 to 40% occur peri-operatively depending on the surgical setting<sup>13, 14</sup>. This varies according to surgical specialty with the majority of the epidemiological literature in cardiac and vascular surgery<sup>15</sup>. We have shown rates of AKI vary depending on the surgical setting ranging from 6% in orthopaedic surgery to 25% in vascular surgery. This suggests that the patients undergoing vascular surgery are already at risk of developing AKI. Factors which may contribute to this predisposition include age, co-morbidity, use of intravenous contrast for vascular imaging and intervention, renovascular disease and the presence of sepsis. Although gentamicin is included in the vascular surgery policy it is optional and many patients may not receive it as they are deemed "high risk" for developing AKI which may account for the results in vascular patients. In gastrointestinal patients, rates of AKI were increasing prior to the policy change with a slower increase following the policy change. Therefore, although rates of AKI are higher in the post intervention period, this increase cannot be attributed to the policy change so requires investigation into other causes. The large amount of missing data in urology and gynaecology with a difference in testing pre and post intervention threatens the validity of these data. It is however important to note and concerning that a large number of patients



who are attending for major surgical procedures are not having their renal function checked in the pre or post-operative period particularly as the evolving literature indicates an increase in short and long term consequences of AKI in this population. KDIGO AKI guidelines state that major surgery is an exposure for AKI and so these patients should have their serum Creatinine and urine output measured individualising according to their clinical status<sup>16</sup>.

Patients who receive gentamicin prophylaxis are generally undergoing major surgery and so we suggest that minimum standard of care should be that they have their bloods checked pre-operatively and at least 24 hours post-operatively.

The development of AKI is associated with longer hospital in-patient stays and increased mortality<sup>13, 14, 17</sup> as well as greater risk of readmission, development and progression of chronic kidney disease (CKD) and poorer long term survival<sup>18</sup>. Epidemiological data has shown that survivors of AKI have higher long term mortality rates than those patients who survive hospitalization without AKI. This association becomes stronger as the severity of AKI increases but is present in patients with small reversible rises in serum creatinine<sup>18</sup>. There is a lack of therapeutic interventions available once AKI is established. The need for RRT is associated with mortality rates of up to 80%, increased hospital stay and significantly increased cost. Earlier detection and recognition of AKI to prevent progression and the need for RRT is therefore imperative both for short and long term morbidity and mortality as well as economically.

It remains unclear whether gentamicin or flucloxacillin in the doses described, or indeed the combination of both, increased the incidence of AKI in this patient group. None of the patients in our study underwent renal biopsy and so we cannot ascertain the exact mechanism of renal injury. Flucloxacillin is associated with acute interstitial nephritis<sup>19</sup> but this is a relatively uncommon adverse effect. Gentamicin is a direct tubular toxin and toxicity during gentamicin therapy is more commonly observed. Following glomerular filtration some gentamicin remains in the lysosomes of the renal proximal tubular epithelium. With either prolonged dosing or supra-therapeutic levels, the accumulation of the drug increases; it

leaks from the lysosomes entering and damaging mitochondria. This leads to tubular epithelial cell death and the acute tubular necrosis-like picture typical of gentamicin toxicity<sup>20</sup>. It has been shown that the nephrotoxic potential of gentamicin varies according to the population studied. Factors potentially relevant to our population include age, dehydration, pre-existing renal impairment and concomitant diuretics and non-steroidal anti-inflammatory medication <sup>21</sup>. Several recent meta-analyses have shown that the risk of AKI due to aminoglycosides is high when used for the empirical treatment of severe gram positive or gram negative bacterial infections<sup>22-25</sup>. Therefore, the KDIGO AKI guideline recommends that aminoglycosides should not be used for the treatment of infection unless no suitable, less nephrotoxic therapeutic alternatives are available <sup>16</sup>. However, concerns regarding anti-microbial resistance as well as increasing rates of CDI have led to continued widespread gentamicin use. In Scotland, the relatively low levels of resistance to aminoglycosides amongst key pathogens in the therapeutic context described make them attractive agents.

The orthopaedic population was older with a mean age of 71 years but the median baseline serum creatinine was 77µmol/l (IQR 64 to 92) indicating that pre-operative renal function was preserved. 36% of the orthopaedic population were prescribed a NSAID in the year before surgery and 39% was prescribed a diuretic. However, we adjusted for these factors in our analysis.

We have demonstrated that a change in prophylactic antibiotic policy to flucloxacillin (2 doses of 1g) and single dose gentamicin (4mg/kg) was associated with increased rates of AKI in patients undergoing orthopaedic implant surgery. We postulate that this is due to the fact that they are a high risk population for developing AKI so greater attention to all modifiable risk factors including prophylactic antibiotic choice is vital in the peri-operative period in order to reduce AKI risk in this vulnerable patient group. The findings of this study has led to a change in the national antibiotic policy recommendation for orthopaedic surgical prophylaxis in Scotland and so demonstrating the importance of measuring unintended

consequences of healthcare interventions. It is therefore planned for this study to be repeated across other health boards in Scotland. We have also highlighted that rates of AKI in vascular surgery are high and AKI is rising in gastrointestinal surgery. Furthermore, it is concerning that there was a lack of testing for AKI in urology and gynaecology surgery. Greater awareness and increased testing for this potentially reversible condition is vital.

## **Methods**

All adults over 18 years resident in or who died in the NHS Tayside region and who underwent surgical procedures where the revised surgical prophylaxis policy included gentamicin as part of a prophylactic antibiotics regime (Table 2) between 1<sup>st</sup> October 2006 and 30<sup>th</sup> September 2010 were included. This study period encompassed two years before and after the change in the antibiotic policy. Cases were identified by the operation procedure codes (OPCS) from hospital admissions data (Appendix Table1). Table 1 shows the recommended antibiotics and doses before and after the policy change. The primary definition of post-operative renal impairment used was the Kidney Disease Improving Global Outcomes (KDIGO) criteria<sup>16</sup>. This was applied using baseline serum creatinine as pre-measurement (most recent prior to surgery) and maximal serum creatinine during the first seven post-operative days as post measurement. Patients with post-operative AKI were classified according to their most severe degree of AKI. Stage 1 was defined as increase in serum creatinine of  $\geq 26.4\mu\text{mol/l}$  or increase to 150% to 200% of baseline. Stage 2 was an increase in serum creatinine to 200% to 300% of baseline value and stage 3 was an increase in serum creatinine to more than 300% of baseline or serum creatinine of  $\geq 354\mu\text{mol/l}$  or initiation of RRT.

Data were linked using the Health Informatics Centre (HIC)<sup>26</sup>, University of Dundee. HIC enables anonymised health record linkage from the population of Tayside (400,000), Scotland, using a unique identifying Community Health Index (CHI) number. Data were linked between the following relevant datasets: Scottish Morbidity Record of hospital

admissions (SMR01) and OPCS coded procedures; laboratory results and medicines dispensed by community pharmacies.

Age, to the nearest year in the year of surgery and gender was obtained from the CHI register and social deprivation from SIMD (Scottish Index of Multiple Deprivation, linked to post code from CHI register).

A Charlson Comorbidity Index (CCI)<sup>27</sup> was calculated for each patient from hospital discharge codes and the number of dispensed prescriptions from community pharmacies in the previous year was applied as an additional measure of comorbidity. Exposure to medicines in the previous year that predispose to renal impairment (non-steroidal anti-inflammatory drugs (NSAIDs), Cox-2 inhibitors, ACE-inhibitors, Angiotensin-II receptor antagonists, diuretics, and beta-blockers) was ascertained from dispensed prescribing data.

Baseline renal function was obtained from the laboratory database. This was the most recent, pre-operative serum creatinine and could include pre-operative samples taken during the current admission for elective surgery but patients undergoing emergency surgery may have AKI on admission to hospital as a result of trauma. We therefore used the most recent serum creatinine prior to admission for emergency patients to distinguish chronic kidney disease from AKI. Only patients with pre and post-operative creatinine measurements could be included, so we measured and reported the completeness of data in each group. Patients on renal replacement therapy (RRT) were excluded from the analysis.

## **Statistical Methods**

Data from each surgical speciality (orthopaedics, urology, vascular surgery and obstetrics and gynaecology) were analysed separately. The design was an interrupted time series (ITS) study with segmented regression analysis<sup>28</sup> using 24 monthly time points before and after the intervention in October 2008. The analysis plan included information that addressed the common risks of bias in ITS studies (Appendix table I). The monthly rates of AKI were defined by the number of cases of each AKI stage as a proportion of all those aged 18 or

older undergoing surgery in each month. Rates were plotted over time for descriptive purposes and the functional form of the relationship pre and post intervention assessed with splines. Rates were analysed using multiple linear regression if the functional form was linear. Where monthly rates were not normally distributed, log transformation was used in the linear regression models to conform to the statistical criterion of normal distribution of residuals. All models were tested for autocorrelation using the Durbin-Watson statistic<sup>29</sup>. Multivariate analyses including age, gender, nephrotoxic drugs and co-morbidity were carried out only when there was a significant change in AKI post intervention. Data for chronic nephrotoxic medication use were adjusted at an aggregate level. Poisson regression analysis was used when there were no or few cases for certain months. In Poisson regression, the outcome variable is in the form of counts or number of cases and the natural log of the denominator (total number of operations) were included in the model as an offset. Analyses were carried out in IBM SPSS (v21) and SAS (v 9.2.1).

### **Ethical Approval**

Anonymised record linkage was conducted according to HIC Standard Operating Procedure (SOP). The Tayside Research Ethics Committee does not require submission of individual studies that follow this SOP. We obtained permission from NHS Tayside's Caldicott Guardian to identify patients who had severe post-operative AKI so that their case notes could be reviewed.

### **Acknowledgement**

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### **Conflict of Interest**

The authors declare no conflict of interest.

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## Figure Legends

Figure 1a: Percentage of AKI (adjusted) Stages 1, 2 and 3 for each month (excluding NOF).

Figure 1b: Percentage of AKI –stage 1, 2 and 3 for each month in fracture NOF cases. The most severe AKI stage was used for this analysis.

Table 1: Descriptive data for other surgical specialities

		Orthopaedics		Urology		Vascular Surgery		Gastrointestinal Surgery		Gynaecology	
Intervention		Before	After	Before	After	Before	After	Before	After	Before	After
Recommended Antibiotics		Cefuroxime (1.5g)	Flucloxacillin (1g) x2 + gentamicin  (4mg/kg)	Co-amoxiclav (1.2g)	Gentamicin (4mg/kg)	Co-amoxiclav (1.2g)	Flucloxacillin (1g) x2 + metronidazole  (500mg) +/- gentamicin (4mg/kg)	Co-amoxiclav (1.2g)	Metronidazole (500mg)  + gentamicin (4mg/kg)	Co-amoxiclav (1.2g)	Metronidazole (500mg)  + gentamicin (4mg/kg)
Number of patients		3674	3992	421	402	358	362	1599	1672	176	227
Mean age (SD)		71.2 (13.5)	70.7 (13.9)	71.4 (12.5)	70.0 (13.1)	70.0 (11.3)	69.0 (12.9)	62.1 (15.9)	61.8 (16.3)	54.9 (13.7)	53.5 (13.7)
Baseline Serum Creatinine (µmol/l)*  median (IQR)		79.0  (66.0, 94.0)	75.0  (62.0, 90.0)	92.0  (77.0, 114.0)	90.0  (74.0, 114.0)	89.5  (75.0, 113.0)	84.0  (67.0, 108.0)	75.0  (62.0, 89.0)	71.0  (60.0, 85.0)	71.0  (61.0, 83.0)	65.0  (58.0, 75.0)
Gender (%)	F	2359 (64.2)	2451 (61.4)	101 (24.0)	87 (21.6)	117 (32.7)	241 (67.3)	953 (57.0)	902 (56.4)	176 (100)	227(100)
	M	1315 (35.8)	1541 (38.6)	320 (76.0)	315 (78.4)	241 (67.3)	234 (64.6)	719 (43.0)	697 (43.6)	0	0
SIMD (%)	1 – 3	706 (19.4)	788 (20.0)	88 (21.2)	108 (27.2)	111 (31.2)	104 (29.0)	402 (24.4)	352 (22.4)	40 (23.0)	59 (26.0)
	4 - 7	1616 (44.5)	1716 (43.6)	176 (42.4)	161 (40.6)	143 (40.2)	151 (42.1)	682 (41.4)	676 (43.1)	70 (40.2)	100 (44.1)
	8 – 10	1311 (36.1)	1429 (36.3)	151 (36.4)	128 (32.2)	102 (28.7)	104 (29.0)	565 (34.3)	541 (34.5)	64 (36.8)	68 (30.0)
CCI (%)	Low (0 or 1)	3494 (95.1)	3774 (94.5)	206 (48.9)	230 (57.2)	244 (68.2)	236 (65.2)	951 (59.5)	1040 (62.2)	122 (69.3)	152 (67.0)
	Medium (2)	121 (3.3)	145 (3.6)	185 (43.9)	128 (31.8)	68 (19.0)	73 (20.2)	432 (27.0)	425 (25.4)	45 (25.6)	65 (28.6)
	High (3+)	59 (1.6)	73 (1.8)	30 (7.1)	44 (10.9)	46 (12.8)	53 (14.6)	216 (13.5)	207 (12.4)	9 (5.1)	10 (4.4)



Table 2: Completeness of creatinine data

Operation	Pre policy change	Post policy change	Chi-square (p-value)	Pre-operative	Post-operative	Pre & Post
	Number of cases with creatinine data (%)					
All Orthopaedic NOF	3674 (81)	4009 (82)	3.68 (0.05)	8883 (94.5)	7917 (84.2)	7698 (81.9)
Urology	421 (58)	402 (52)	<b>4.38 (0.04)</b>	1396 (92.9)	828 (55.1)	823 (54.8)
Vascular	358 (89)	362 (86)	2.00 (p=0.16)	798 (96.8)	727 (88.2)	720 (87.4)
Gastrointestinal	1599 (78)	1672 (78)	0.50 (p=0.48)	4089 (97.6)	3315 (79.2)	3271 (78.1)
Gynaecology	176 (35)	227 (47)	<b>12.76 (&lt;0.001)</b>	927 (94.2)	423 (43.0)	403 (41.0)



Table 4: ITS of monthly percentage of AKI in orthopaedic surgery using pre vs. highest post-operative Creatinine measurement - excluding cases with NOF fracture

Variables	$\beta$ (95% Confidence Interval)	p
Time	0.08 (-0.12 to 0.28)	0.40
Intervention (0 = pre policy change , 1 = post policy change)	-1.65 (-5.45 to 2.16)	0.39
Time after intervention	0.30 (0.01 to 0.59)	0.04
Percentage of males (+1%)	-0.07 (-0.30 to 0.16)	0.52
Mean age (+1 year)	0.09 (-0.69 to 0.88)	0.81
Percentage of Beta-blockers (+1%)	-3.85 (-8.24 to 0.54)	0.08